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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/942,052	RAITANO ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence alignments pp. 1-3*.

DETAILED ACTION

1. Claims 1-87 have been cancelled.

Claims 88-98 have been added.

2. Claims 88-98 are pending are under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

5. The objection to the Oath/Declaration for containing non-initialed and/or non-dated alterations to the address of inventor Arthur B. Raitano is withdrawn in view of the filing of an ADS under 37 CFR 1.76.

6. The objection to claim 4 as being drawn to non-elected inventions is withdrawn in view of the cancellation of claim 4.

7. All previous rejections in the Office Action mailed 12/12/2003 are withdrawn in view of the Newly added claims and the New Grounds of Rejections below.

Response to Arguments

8. The objection to the specification for containing embedded hyperlinks and/or other form of browser-executable code is maintained.

The response filed 5/21/2004 amended the specification to remove the embedded hyperlinks, however, the amendments to the specification did not remove the

browser-executable code. For example, www.expasy.ch/tools/ is an active hyperlink (browser-executable code) because clicking on it brings you to that particular web site.

Appropriate correction is required.

New Grounds of Rejections

Specification

9. The disclosure is objected to because of the following informalities:

a. The titles for Examples 13, 36 and 37 contain typos that need correction.

b. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

10. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 88-98 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 88, as written, does not sufficiently distinguish an antibody that binds SEQ ID NO:728 as it exists naturally because the

claims do not particularly point out any non-naturally occurring differences between the claimed antibody and the naturally occurring antibody. The claimed antibody (not antigen binding fragments) reads upon antibodies as they are naturally synthesized in eukaryotic cells.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1996)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F. Supp 68 (1967), 155 U.S.P.Q. 139, (District Court, New Jersey, 1967)). Base claim 88 should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

11. Claims 88-98 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The claims are drawn to an antibody or fragment thereof that specifically binds to a protein having at least 90% homology to SEQ ID NO:728, wherein the antibody is a monoclonal, human, humanized, or chimeric antibody and the antibody fragment thereof is a Fab, F(ab)2, Fv or sFv fragment and the antibody is conjugated to a diagnostic agent or a cytotoxic agent and the antibody further comprises a pharmaceutically acceptable carrier. The utility and enablement of the antibody depends upon whether or

not the polypeptide it binds has utility and enablement. The specification discloses that the polypeptide of SEQ ID NO:728 is identical to the human opa-interacting protein (OIP5) (see Figure 3 and Example 41 at page 126) and shares homology to thyroid hormone receptor interacting protein-6 (TRIP6), which is an intracellular signaling molecule that relays information to the nucleus thereby regulating gene expression (see page 126). The specification generally asserts that 85P1B3 (SEQ ID NO:728) will be useful for a number of purposes; however, none of these asserted uses meet a specific and substantial asserted utility or a well-established utility. The asserted utilities will each be addressed in turn.

1) the 85P1B3 polypeptide can be used to isolate other molecules that interact with 85P1B3: This asserted utility is not specific or substantial. Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed polypeptide of SEQ ID NO:728. Furthermore, since the specification does not disclose how SEQ ID NO:728 or its binding partners can be used, significant further research would be required of the skilled artisan to determine how to use the claimed polypeptide or its binding partner. Since the asserted utility is not presented in a ready to use, real-world application, the asserted utility is not substantial.

2) the 85P1B3 polypeptide can be used as a diagnostic: This asserted utility is not specific or substantial. With the exception of a few housekeeping genes, all polypeptides have a tissue specific pattern of expression, and thus virtually any polypeptide can be used as a diagnostic. Thus, the asserted utility is not specific to the polypeptide of SEQ ID NO:728. Furthermore, since the specification does not disclose

the tissue or cell-specific or disease-specific expression of the polypeptide of SEQ ID NO:728, significant further research would be required of the skilled artisan to determine the tissue-specific expression of the polypeptide of SEQ ID NO:728, its association with a particular disease state empirically and how to use the claimed polypeptide. Since the asserted utility is not presented in a ready to use, real-world application, the asserted utility is not substantial.

3) the 85P1B3 polypeptide can be used in therapy (i.e., induction of an immune response or as a vaccine composition): This asserted utility is not specific or substantial. Since a defect in any polypeptide is likely to cause a disease of some sort, every polypeptide is a target for drug development. Thus, the asserted utility is not specific to the claimed polypeptide of SEQ ID NO:728. Furthermore, the specification does not disclose a nexus between any specific disease state and a change in amount or form of the polypeptide of SEQ ID NO:728 (not the mRNA). Significant further research would have to be conducted to identify such a nexus. Therefore, the asserted utility is not substantial.

The specification also discloses the detection of 85P1B3 (SEQ ID NO:728) mRNA in human patient cancer specimens such as cancers of the breast, prostate, uterus, cervix, stomach and lung (see Figures 13-16). This information provides a credible, specific and substantial utility for 85P1B3 nucleic acids, but not for the polypeptide of SEQ ID NO:728 or antibodies that bind said polypeptide. The literature reports that it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression, such that the

claimed antibodies that bind the recited polypeptide of SEQ ID NO:728 would be useful for diagnosis of cancer or as a drug target. For example, Pennica et al. (1998, PNAS USA 95:14717-14722) disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISP*s in Human Colon Tumors." See also Konopka (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that

> "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract).

Finally, even if gene amplification correlates with increased transcription, it does not always follow that protein levels are also amplified. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into protein abundances, which varied more than so-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Therefore, the art indicates that it is not the norm that gene amplification, or even increased transcription, results in increased polypeptide levels.

Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. In fact, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For example, Lewin B. (Genes

VI, 1997, CH. 29, pp. 847-848) acknowledges that control of gene expression can occur at multiple stages, and that production of RNA *cannot inevitably* be equated with production of protein, it is clear that overwhelming majority of regulatory events occur at the initiation of transcription (see page 847, right column). The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar et al (Cancer Research, 2001, 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isoenzyme expression is likely regulated at the posttranscriptional/translational level" (see abstract). Gokman-Polar et al show in figures 6 and 7 that there is no increase in mRNA expression for any of the isoenzymes, while the protein is significantly overexpressed as shown by figures 4 and 5. These references serve to demonstrate that the analysis of levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression.

Therefore, the asserted utility is not substantial, as the real-world use has not been established. Thus, the proposed use of the claimed antibodies that bind SEQ ID NO:728 are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-

where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license" "[i]t is not a reward for the search, but compensation for its successful conclusion."

12. Claims 88-98 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

13. Claims 88-98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an antibody or fragment thereof that specifically binds to a protein at least 90% homology to SEQ ID NO:728. The specification discloses only the human 85P1B3 polypeptide (SEQ ID NO:728). The specification discloses that naturally occurring allelic variants share at least 90% homology with human 85P1B3 (i.e., SEQ ID NO:728) (see page 24). The specification does not disclose any polypeptide that is at least 90% homologous to SEQ ID NO:728 except SEQ ID NO:728.

The general knowledge in the art concerning homologous proteins does not provide any indication of how the structure of one homolog is representative of unknown homologs. Reiger et al. (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences that would be at least 90% homologous to the protein of SEQ ID NO:728 are not defined. With the exception of SEQ ID NO:728 the skilled artisan cannot envision the detailed structure of the encompassed homologous proteins and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the

method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddles v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddles*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the protein comprising the sequence set forth in SEQ ID NO:728, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

14. Claims 88-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody or fragment thereof that specifically binds to a protein comprising SEQ ID NO:728, does not reasonably provide enablement for an antibody or fragment thereof that specifically binds to a protein having at least 90% homology to SEQ ID NO:728. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to an antibody or fragment thereof that specifically binds to a protein having at least 90% homology to SEQ ID NO:728, wherein the antibody is a monoclonal, human, humanized, or chimeric antibody and the antibody fragment thereof is a Fab, F(ab)2, Fv or sFv fragment and the antibody is conjugated to a diagnostic agent or a cytotoxic agent and the antibody further comprises a pharmaceutically acceptable carrier. The specification teaches the polypeptide of SEQ ID NO:728 (i.e., 85P1B3), which is identical to the human opa-interacting protein (OIP5) (see Figure 3 and Example 41 at page 126). The specification has not taught any protein that is at least 90% homologous to SEQ ID NO:728 (85P1B3) or any antibody that binds to such protein or the use of such antibody.

The specification does not teach how to make or use the claimed variant proteins, which are defined by the specification as allelic variants, homologs, analogs as well as variants that include conservative substitutions (see page 23). This does not provide sufficient, specific guidance, enabling the skilled artisan to make and/or use the invention without undue experimentation. The specification does not disclose the

extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar biological activity are limited in any protein. The result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modifications in such proteins. The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

a. The general tolerance to modification and extent of such tolerance;

b. The specific positions and regions of the sequence which can be predictably modified and which regions are critical;

c. What fragments, if any, can be made which retain the biological activity of the intact protein; and

d. The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).f.

Furthermore, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5

times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987).

Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other activities when constructing analogs (see entire document).

Coleman P. M. (Research in Immunology, 145:33-36, 1994) discloses that even single amino acid changes within the interface of an antibody-antigen complex can alter the interaction by driving the affinity towards more tightly bound complexes or effectively abolish the interaction entirely (see page 33).

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. The art of protein chemistry remains very unpredictable as Burgess et al, Lazar et al, Schwartz et al, Lederman et al, Li et al and Coleman P. M. conclusively demonstrate.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of homologous proteins (i.e., 90% homologous to SEQ ID NO:728) as well as antibodies that bind such proteins as encompassed by the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Priority

15. Because the claimed subject matter does not have a specific and substantial asserted utility or a well established utility, the priority date of the claims are given the filing date of the instant application, 8/28/01.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 88-95 and 97-98 are rejected under 35 U.S.C. 102(e) as being anticipated by Tang et al (WO 01/53312, 102(e) date 1/21/2000, Ids filed 2/11/2003).

The claims are drawn to an antibody or fragment thereof that specifically binds to a protein having at least 90% homology to SEQ ID NO:728, wherein the antibody is a monoclonal, human, humanized, or chimeric antibody and the antibody fragment thereof is a Fab, F(ab)2, Fv or sFv fragment and the antibody is conjugated to a diagnostic agent or a cytotoxic agent and the antibody further comprises a pharmaceutically acceptable carrier.

Tang et al teach antibodies that bind the polypeptides of SEQ ID NO:3368 and SEQ ID NO:6940, which share 100% amino acid identity with the polypeptide of SEQ ID NO:728 (see alignments attached to this office action). Tang et al teach monoclonal, human and humanized antibodies and antibody fragments such as Fab, F(ab)2 a and Fv fragments (see pages 76-80). Tang et al teach immunoconjugates comprising an antibody and a cytotoxic agent such as a chemotherapeutic agent, toxin, or a radioactive isotope including diphtheria toxin, exotoxin A chain, ricin A chain, abrin A chain, ^{131}I, ^{90}Y and ^{186}Re (see pages 83-84). Tang et al teach pharmaceutical compositions (pages 63-71) comprising a suitable carrier or excipient and an antibody that binds the polypeptides of SEQ ID NOS:3368 and 6940 which share 100% amino acid identity with the polypeptide of SEQ ID NO:728 (see alignments attached to this office action).

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 88-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (Molecular Microbiology 27(1):171-186, 1998) and in view of Campbell A. M. (Monoclonal Antibody Technology, Elsevier Science Publishers, NY, chapter 1, pages 1-32, 1986) and Queen et al (5,530,101, 6/25/1996) and Reiter et al (U.S. Patent 6,261,791 B1, 5/25/1999).

The claims are drawn to an antibody or fragment thereof that specifically binds to a protein having at least 90% homology to SEQ ID NO:728, wherein the antibody is a monoclonal, human, humanized, or chimeric antibody and the antibody fragment thereof is a Fab, F(ab)2, Fv or sFv fragment and the antibody is conjugated to a diagnostic agent or a cytotoxic agent and the antibody further comprises a pharmaceutically acceptable carrier.

Williams et al teach the OIP5 polypeptide, which is identical (100% amino acid identity) to the polypeptide of SEQ ID NO:728 (see the alignment attached to the back of this Office Action) (see Table 2). Williams et al do not specifically teach an antibody that binds the polypeptide of SEQ ID NO:728 (OIP5) or antibody conjugates comprising diagnostic or cytotoxic agents or a pharmaceutically acceptable carrier as instantly claimed. These deficiencies are made up for in the teachings of Campbell and Queen et al and Reiter et al.

Campbell A. M. teaches monoclonal antibodies to polypeptides.

Queen et al teach human, chimeric, humanized antibodies (see columns 2-3, 11-16). Queen et al teach antibody conjugates comprising cytotoxic agents such as Iodine-131, Yttrium-90, Rhenium-188 and Bismuth-212 or other alpha emitters, chemotherapeutic agents and cytotoxic proteins such as pseudomonas exotoxin A, ricin, diphtheria toxin and ricin A chain as well as antibody fragments such as Fab (see column 20, lines 1-22). Queen et al also teach pharmaceutical compositions comprising an antibody and a pharmaceutically acceptable carrier (see columns 23-24).

Reiter et al teach monoclonal, chimeric and humanized antibodies and antibody fragments such as Fab, Fab' and F(ab)2 as well as immunoconjugates comprising cytotoxic agents such as taxol, etoposide, vincristine, vinblastine, colchicines, actinomycin, diphteria toxin, Pseudomonas exotoxin (PE) A, PE40, abrin and radioisotopes (see entire document, particularly column 14, columns 16-17).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a monoclonal antibody to the

polypeptide of Williams et al by the method of Campbell A. M and to produce a chimeric antibody, a humanized antibody, antibody fragments as well as immunoconjugates comprising cytotoxic agents as taught by Queen et al and Reiter et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a monoclonal antibody to the polypeptide of Williams et al by the method of Campbell A. M and to produce a chimeric antibody, a humanized antibody, antibody fragments as well as immunoconjugates comprising cytotoxic agents as taught by Queen et al and Reiter et al because Campbell A. M. teach "it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (see page 29) and Queen et al and Reiter et al teach chimeric and humanized antibodies as well as immunoconjugates comprising cytotoxic agents. Thus, it would have been obvious to one of skill in the art at the time the invention was made to have produced a monoclonal antibody to the polypeptide of Williams et al by the method of Campbell A. M and to produce a chimeric antibody, a humanized antibody, antibody fragments as well as immunoconjugates comprising cytotoxic agents as taught by Queen et al and Reiter et al for basic research. Lastly, the Board of Patent Appeals and interferences has taken the position that once an antigen has been isolated, the manufacture of monoclonal antibodies against it is *prima facie* obvious. See Ex parte Ehrlich, 3USPQ 2d 1011 (PTO Bd. Pat. APP. & Int. 1987), Ex parte Sugimoto, 14 USPQ 2d 1312 (PTO Bd. Pat. APP. & Int. 1990).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

20. Claims 88-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al (WO 01/53312, 102(e) date 1/21/2000, Ids filed 2/11/2003) in view of Reiter et al (U.S. Patent 6,261,791 B1, 5/25/1999).

The claims have been described supra.

Tang et al have been described supra.

Reiter et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have conjugated the antibodies taught by Tang et al with the cytotoxic agents such as taxol, etoposide, vincristine, vinblastine, colchicines and actinomycin as taught by Reiter et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have conjugated the antibodies taught by Tang et al with the cytotoxic agents such as taxol, etoposide, vincristine, vinblastine, colchicines and actinomycin as taught by Reiter et al because Tang et al teach antibodies that bind a polypeptide (SEQ ID NO:3368 or SEQ ID NO: 6940) that is identical to the polypeptide of SEQ ID NO:728 and immunoconjugates comprising said antibodies conjugated to a cytotoxic agent and Reiter et al teach immunoconjugates comprising cytotoxic agents such as taxol, etoposide, vincristine, vinblastine, colchicines, actinomycin. Thus, it would have been obvious to one of skill in the art at the time the

invention was made to have conjugated the antibodies taught by Tang et al with the cytotoxic agents such as taxol, etoposide, vincristine, vinblastine, colchicines and actinomycin as taught by Reiter et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

21. No claim is allowed.

22. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER

```
RESULT 1
OIP5_HUMAN
ID   OIP5_HUMAN     STANDARD;      PRT;   229 AA.
AC   O43482; Q96BX7;
DT   28-FEB-2003 (Rel. 41, Created)
DT   28-FEB-2003 (Rel. 41, Last sequence update)
DT   10-OCT-2003 (Rel. 42, Last annotation update)
DE   Opa-interacting protein 5.
GN   OIP5.
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   SEQUENCE FROM N.A.
RX   MEDLINE=98125741; PubMed=9466265;
RA   Williams J.M., Chen G.-C., Zhu L., Rest R.F.;
RT   "Using the yeast two-hybrid system to identify human epithelial cell
RT   proteins that bind gonococcal Opa proteins: intracellular gonococci
RT   bind pyruvate kinase via their Opa proteins and require host pyruvate
RT   for growth.";
RL   Mol. Microbiol. 27:171-186(1998).
RN   [2]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Uterus;
RX   MEDLINE=22388257; PubMed=12477932;
RA   Strausberg R.L., Feingold E.A., Grouse L.H., Derge J.G.,
RA   Klausner R.D., Collins F.S., Wagner L., Shenmen C.M., Schuler G.D.,
RA   Altschul S.F., Zeeberg B., Buetow K.H., Schaefer C.F., Bhat N.K.,
RA   Hopkins R.F., Jordan H., Moore T., Max S.I., Wang J., Hsieh F.,
RA   Diatchenko L., Marusina K., Farmer A.A., Rubin G.M., Hong L.,
RA   Stapleton M., Soares M.B., Bonaldo M.F., Casavant T.L., Scheetz T.E.,
RA   Brownstein M.J., Usdin T.B., Toshiyuki S., Carninci P., Prange C.,
RA   Raha S.S., Loquellano N.A., Peters G.J., Abramson R.D., Mullahy S.J.,
RA   Bosak S.A., McEwan P.J., McKernan K.J., Malek J.A., Gunaratne P.H.,
RA   Richards S., Worley K.C., Hale S., Garcia A.M., Gay L.J., Hulyk S.W.,
RA   Villalon D.K., Muzny D.M., Sodergren E.J., Lu X., Gibbs R.A.,
RA   Fahey J., Helton E., Ketteman M., Madan A., Rodrigues S., Sanchez A.,
RA   Whiting M., Madan A., Young A.C., Shevchenko Y., Bouffard G.G.,
RA   Blakesley R.W., Touchman J.W., Green E.D., Dickson M.C.,
RA   Rodriguez A.C., Grimwood J., Schmutz J., Myers R.M.,
RA   Butterfield Y.S.N., Krzywinski M.I., Skalska U., Smailus D.E.,
RA   Schnerch A., Schein J.E., Jones S.J.M., Marra M.A.;
RT   "Generation and initial analysis of more than 15,000 full-length
RT   human and mouse cDNA sequences.";
RL   Proc. Natl. Acad. Sci. U.S.A. 99:16899-16903(2002).
CC   -!- SUBUNIT: Binds outer membrane protein OpaP from Neisseria
CC       gonorrhoeae.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use by non-profit institutions as long as its content is in no way
CC   modified and this statement is not removed. Usage by and for commercial
CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; AF025441; AAC39561.1; ALT_INIT.
DR   EMBL; BC015050; AAH15050.1; -.
DR   MIM; 606020; -.
DR   GO; GO:0005515; F:protein binding; TAS.
DR   GO; GO:0007154; P:cell communication; NAS.
SQ   SEQUENCE   229 AA;  24691 MW;  0EBD4006193A3106 CRC64;

  Query Match             100.0%;  Score 1198;  DB 1;  Length 229;
  Best Local Similarity   100.0%;  Pred. No. 2.7e-104;
  Matches  229;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MAAQPLRHRSRCATPPRGDFCGGTERAIDQASFTTSMEWDTQVVKGSSPLGPAGLGAEEP 60
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Db          1 MAAQPLRHRSRCATPPRGDFCGGTERAIDQASFTTSMEWDTQVVKGSSPLGPAGLGAEEP 60

Qy         61 AAGPQLPSWLQPERCAVFQCAQCHAVLADSVHLAWDLSRSLGAVVFSRVTNNVVLEAPFL 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 AAGPQLPSWLQPERCAVFQCAQCHAVLADSVHLAWDLSRSLGAVVFSRVTNNVVLEAPFL 120

Qy        121 VGIEGSLKGSTYNLLFCGSCGIPVGFHLYSTHAALAALRGHFCLSSDKMVCYLLKTKAIV 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 VGIEGSLKGSTYNLLFCGSCGIPVGFHLYSTHAALAALRGHFCLSSDKMVCYLLKTKAIV 180

Qy        181 NASEMDIQNVPLSEKIAELKEKIVLTHNRLKSLMKILSEVTPDQSKPEN 229
              |||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 NASEMDIQNVPLSEKIAELKEKIVLTHNRLKSLMKILSEVTPDQSKPEN 229


RESULT 2
```

RESULT 1
AAM40223
ID AAM40223 standard; protein; 229 AA.
XX
AC AAM40223;
XX
DT 22-OCT-2001 (first entry)
XX
DE Human polypeptide SEQ ID NO 3368.
XX
KW Human; nootropic; immunosuppressant; cytostatic; gene therapy; cancer;
KW peripheral nervous system; neuropathy; central nervous system; CNS;
KW Alzheimer's; Parkinson's disease; Huntington's disease; haemostatic;
KW amyotrophic lateral sclerosis; Shy-Drager Syndrome; chemotactic;
KW chemokinetic; thrombolytic; drug screening; arthritis; inflammation;
KW leukaemia.
XX
OS Homo sapiens.
XX
PN WO200153312-A1.
XX
PD 26-JUL-2001.
XX
PF 26-DEC-2000; 2000WO-US034263.
XX
PR 23-DEC-1999; 99US-00471275.
PR 21-JAN-2000; 2000US-00488725.
PR 25-APR-2000; 2000US-00552317.
PR 20-JUN-2000; 2000US-00598042.
PR 19-JUL-2000; 2000US-00620312.
PR 03-AUG-2000; 2000US-00653450.
PR 14-SEP-2000; 2000US-00662191.
PR 19-OCT-2000; 2000US-00693036.
PR 29-NOV-2000; 2000US-00727344.
XX
PA (HYSE-) HYSEQ INC.
XX
PI Tang YT, Liu C, Asundi V, Chen R, Ma Y, Qian XB, Ren F, Wang D;
PI Wang J, Wang Z, Wehrman T, Xu C, Xue AJ, Yang Y, Zhang J, Zhao QA;
PI Zhou P, Goodrich R, Drmanac RT;
XX
DR WPI; 2001-442253/47.
DR N-PSDB; AAI59379.
XX
PT Novel nucleic acids and polypeptides, useful for treating disorders such
PT as central nervous system injuries.
XX
PS Example 5; SEQ ID NO 3368; 10078pp; English.
XX
CC The invention relates to human nucleic acids (AAI57798-AAI61369) and the
CC encoded polypeptides (AAM38642-AAM42213) with nootropic,
CC immunosuppressant and cytostatic activity. The polynucleotides are useful
CC in gene therapy. A composition containing a polypeptide or polynucleotide
CC of the invention may be used to treat diseases of the peripheral nervous
CC system, such as peripheral nervous injuries, peripheral neuropathy and
CC localised neuropathies and central nervous system diseases, such as
CC Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic
CC lateral sclerosis, and Shy-Drager Syndrome. Other uses include the
CC utilisation of the activities such as: Immune system suppression,
CC Activin/inhibin activity, chemotactic/chemokinetic activity, haemostatic
CC and thrombolytic activity, cancer diagnosis and therapy, drug screening,
CC assays for receptor activity, arthritis and inflammation, leukaemias and
CC C.N.S disorders. Note: The sequence data for this patent did not form
CC part of the printed specification
XX
SQ Sequence 229 AA;

Query Match 100.0%; Score 1198; DB 4; Length 229;
Best Local Similarity 100.0%; Pred. No. 5.2e-127;
Matches 229; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 MAAQPLRHRSRCATPPRGDFCGGTERAIDQASFTTSMEWDTQVVKGSSPLGPAGLGAEEP 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MAAQPLRHRSRCATPPRGDFCGGTERAIDQASFTTSMEWDTQVVKGSSPLGPAGLGAEEP 60

Qy         61 AAGPQLPSWLQPERCAVFQCAQCHAVLADSVHLAWDLSRSLGAVVFSRVTNNVVLEAPFL 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 AAGPQLPSWLQPERCAVFQCAQCHAVLADSVHLAWDLSRSLGAVVFSRVTNNVVLEAPFL 120

Qy        121 VGIEGSLKGSTYNLLFCGSCGIPVGFHLYSTHAALAALRGHFCLSSDKMVCYLLKTKAIV 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 VGIEGSLKGSTYNLLFCGSCGIPVGFHLYSTHAALAALRGHFCLSSDKMVCYLLKTKAIV 180

Qy        181 NASEMDIQNVPLSEKIAELKEKIVLTHNRLKSLMKILSEVTPDQSKPEN 229
              |||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 NASEMDIQNVPLSEKIAELKEKIVLTHNRLKSLMKILSEVTPDQSKPEN 229
```

ID AAM42009 standard; protein; 231 AA.
XX
AC AAM42009;
XX
DT 22-OCT-2001 (first entry)
XX
DE Human polypeptide SEQ ID NO 6940.
XX
KW Human; nootropic; immunosuppressant; cytostatic; gene therapy; cancer;
KW peripheral nervous system; neuropathy; central nervous system; CNS;
KW Alzheimer's; Parkinson's disease; Huntington's disease; haemostatic;
KW amyotrophic lateral sclerosis; Shy-Drager Syndrome; chemotactic;
KW chemokinetic; thrombolytic; drug screening; arthritis; inflammation;
KW leukaemia.
XX
OS Homo sapiens.
XX
PN WO200153312-A1.
XX
PD 26-JUL-2001.
XX
PF 26-DEC-2000; 2000WO-US034263.
XX
PR 23-DEC-1999; 99US-00471275.
PR 21-JAN-2000; 2000US-00488725.
PR 25-APR-2000; 2000US-00552317.
PR 20-JUN-2000; 2000US-00598042.
PR 19-JUL-2000; 2000US-00620312.
PR 03-AUG-2000; 2000US-00653450.
PR 14-SEP-2000; 2000US-00662191.
PR 19-OCT-2000; 2000US-00693036.
PR 29-NOV-2000; 2000US-00727344.
XX
PA (HYSE-) HYSEQ INC.
XX
PI Tang YT, Liu C, Asundi V, Chen R, Ma Y, Qian XB, Ren P, Wang D;
PI Wang J, Wang Z, Wehrman T, Xu C, Xue AJ, Yang Y, Zhang J, Zhao QA;
PI Zhou P, Goodrich R, Drmanac RT;
XX
DR WPI; 2001-442253/47.
DR N-PSDB; AAI61165.
XX
PT Novel nucleic acids and polypeptides, useful for treating disorders such
PT as central nervous system injuries.
XX
PS Example 2; SEQ ID NO 6940; 10078pp; English.
XX
CC The invention relates to human nucleic acids (AAI57798-AAI61369) and the
CC encoded polypeptides (AAM38642-AAM42213) with nootropic,
CC immunosuppressant and cytostatic activity. The polynucleotides are useful
CC in gene therapy. A composition containing a polypeptide or polynucleotide
CC of the invention may be used to treat diseases of the peripheral nervous
CC system, such as peripheral nervous injuries, peripheral neuropathy and
CC localised neuropathies and central nervous system diseases, such as
CC Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic
CC lateral sclerosis, and Shy-Drager Syndrome. Other uses include the
CC utilisation of the activities such as: Immune system suppression,
CC Activin/inhibin activity, chemotactic/chemokinetic activity, haemostatic
CC and thrombolytic activity, cancer diagnosis and therapy, drug screening,
CC assays for receptor activity, arthritis and inflammation, leukaemias and
CC C.N.S disorders. Note: The sequence data for this patent did not form
CC part of the printed specification
XX
SQ Sequence 231 AA;

Query Match 100.0%; Score 1198; DB 4; Length 231;
Best Local Similarity 100.0%; Pred. No. 5.3e-127;
Matches 229; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 MAAQPLRHRSRCATPPRGDFCGGTERAIDQASFTTSMEWDTQVVKGSSPLGPAGLGAEEP 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          3 MAAQPLRHRSRCATPPRGDFCGGTERAIDQASFTTSMEWDTQVVKGSSPLGPAGLGAEEP 62

Qy         61 AAGPQLPSWLQPERCAVFQCAQCHAVLADSVHLAWDLSRSLGAVVFSRVTNNVVLEAPFL 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         63 AAGPQLPSWLQPERCAVFQCAQCHAVLADSVHLAWDLSRSLGAVVFSRVTNNVVLEAPFL 122

Qy        121 VGIEGSLKGSTYNLLFCGSCGIPVGFHLYSTHAALAALRGHFCLSSDKMVCYLLKTKAIV 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||

Db        123 VGIEGSLKGSTYNLLFCGSCGIPVGFHLYSTHAALAALRGHFCLSSDKMVCYLLKTKAIV 182

Qy        181 NASEMDIQNVPLSEKIAELKEKIVLTHNRLKSLMKILSEVTPDQSKPEN 229
              |||||||||||||||||||||||||||||||||||||||||||||||||
Db        183 NASEMDIQNVPLSEKIAELKEKIVLTHNRLKSLMKILSEVTPDQSKPEN 231
```

3